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Early planned removal versus expectant management of peripherally inserted central catheters to prevent infection in newborn infants (Review)

Gordon A, Greenhalgh M, McGuire W

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[Intervention Review]

Early planned removal versus expectant management of peripherally inserted central catheters to prevent infection in newborn infants

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ABSTRACT

Background

Duration of use may be a modifiable risk factor for central venous catheter-associated bloodstream infection in newborn infants. Early planned removal of peripherally inserted central catheters (PICCs) is recommended as a strategy to reduce the incidence of infection and its associated morbidity and mortality.

Objectives

To determine the effectiveness of early planned removal of PICCs (up to two weeks after insertion) compared to an expectant approach or a longer fixed duration in preventing bloodstream infection and other complications in newborn infants.

Search methods

We searched of the Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 4), Ovid MEDLINE, Embase, Maternity & Infant Care Database, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (until April 2018), and conference proceedings and previous reviews.

Selection criteria

Randomised and quasi-randomised controlled trials that assessed the effect of early planned removal of umbilical venous catheters (up to two weeks after insertion) compared to an expectant management approach or a longer fixed duration in preventing bloodstream infection and other complications in newborn infants.

Data collection and analysis

Two review authors assessed trial eligibility independently. We planned to analyse any treatment effects in the individual trials and report the risk ratio and risk difference for dichotomous data and mean difference for continuous data, with respective 95% confidence intervals. We planned to use a fixed-effect model in meta-analyses and explore potential causes of heterogeneity in sensitivity analyses. We planned to assess the quality of evidence for the main comparison at the outcome level using "Grading of Recommendations Assessment, Development and Evaluation" (GRADE) methods.

Main results

We did not identify any eligible randomised controlled trials.

Authors' conclusions

There are no trial data to guide practice regarding early planned removal versus expectant management of PICCs in newborn infants. A simple and pragmatic randomised controlled trial is needed to resolve the uncertainty about optimal management in this common and important clinical dilemma.

PLAIN LANGUAGE SUMMARY

Early planned removal versus expectant management of peripherally inserted central catheters to prevent infection in newborn infants

Review question

In newborn infants with a peripherally inserted central catheter in place, does early removal of the catheter reduce the risk of complications, including infection?

Background

Infection in the bloodstream is a frequent and harmful complication for newborn infants who have a peripherally inserted central catheter (a long, narrow, soft and flexible plastic tube inserted through the skin into a vein and advanced several centimetres into the infant's large blood vessels; used as a stable route to deliver drugs and nutrition). Bloodstream infection may cause death and disability. One potential method of reducing the risk of this and other serious complications is to remove the catheter within about two weeks after insertion rather than leaving it for longer until no longer required.

Study characteristics/key results

We did not find any randomised controlled trials that assessed whether removing peripherally inserted central catheters within two weeks prevents infection or other complications in newborn infants.

Conclusions

There are no trial data available to help clinicians to address this common clinical dilemma. Due to the potential for benefit and harm, such a trial may be warranted.

BACKGROUND

Description of the condition

Peripherally inserted central catheters (PICCs), also commonly referred to as percutaneous central venous catheters (CVCs), provide a stable route for the intravenous delivery of drugs or fluids to preterm or sick newborn infants. Typically, PICCs are inserted via a superficial vein in the upper or lower limb, usually avoiding proximal sites such as the femoral or axillary veins, and are then advanced so that the tip of the catheter is sited at the vena caval junction with the right atrium of the heart (Jain 2013; Wrightson 2013). Peripherally inserted central catheters are less expensive and easier to insert than catheters placed directly or via a subcutaneous tunnel into central veins. Because they are more stable than short peripheral cannulae, their use reduces the risk of extravasation injury from hyperosmolar parenteral nutrition solutions and medications (Ainsworth 2015).

Bloodstream infection is the most common serious complication associated with the use of PICCs in newborn infants. The reported incidence ranges from about 2% to 30% depending on the precise diagnostic criteria and the demographics of the population studied (Chien 2002; Cartwright 2004; van der Zwet 2005;

Garland 2008; Hoang 2008; Olsen 2009; O'Grady 2011; Ohki 2013). Very preterm infants are at the highest risk, but inter-unit variation in the incidence of catheter-associated bloodstream infection is not fully explained by case-mix and may relate to care or infection control practices (Wong 2012). Newborn infants, particularly very preterm infants, with an acquired bloodstream infection have a higher risk of mortality and a range of important morbidities including bronchopulmonary dysplasia, necrotising enterocolitis, retinopathy of prematurity, hepatic dysfunction and prolonged hospitalisation (Saint 2000; Mahieu 2001a; Mahieu 2001b; Chapman 2003; Payne 2004; Adams-Chapman 2006; Hermans 2007; Lahra 2009). Bloodstream infection is associated with higher rates of adverse neurodevelopmental outcomes including cognitive or sensory impairment and cerebral palsy (Stoll 2004; Shah 2008a; Bassler 2009).

The most common causes of PICC-associated bloodstream infections in newborn infants are coagulase-negative staphylococci, other Gram-positive cocci (*Staphylococcus aureus* (*S. aureus*), enterococci), Gram-negative bacilli and fungi (predominantly *Candida* species) (Makhoul 2002; O'Grady 2002; Stoll 2002; Isaacs 2003; Isaacs 2004; Gordon 2006; de Brito 2010). Micro-organisms can gain access through the PICC entry site or via the catheter hub into the PICC lumen or tract. Pathogens adhere to the material of the PICC and secrete an intraluminal or extraluminal biofilm of extracellular polymeric substances (Machado 2009). Bacteria or fungi growing within the biofilm are relatively protected from the host's immune system and circulating antimicrobial agents thus enabling sustained colonisation (Ramirez de Arellano 1994; Stewart 2001). It is often necessary to remove the PICC in order to clear the infection (Benjamin 2001). A thrombus (blood clot) attached to the PICC may be an additional nidus (locus) for infection (Thornburg 2008). Some evidence exists that continuous heparin infusion can reduce the incidence of PICC-occlusion in neonates, but the data are insufficient to determine the effect of this intervention on the risk of infection (Shah 2008b).

Several strategies to prevent PICC-associated bloodstream infections have been developed and adopted, often as multifaceted packages of interventions ('care bundles'). These include strict aseptic precautions when inserting and accessing the PICC, use of needleless intravascular catheter systems and prompt removal when the PICC is no longer needed (O'Grady 2002; Yébenes 2004; Pronovost 2006; Borghesi 2008; Miller 2010; Sannoh 2010; Vanholder 2010; Wirtschafter 2010; Kaplan 2011; O'Grady 2011; Schulman 2011). Care bundles have been shown to reduce bloodstream infection rates in adult, paediatric and neonatal intensive care studies (Pronovost 2006; Miller 2010; Wirtschafter 2010; Kaplan 2011; Schulman 2011; Fisher 2013). Despite these strategies, however, PICC-associated infections remain a major cause of morbidity and mortality in newborn infants and other interventions are required to reduce the infection rates further.

Description of the intervention

Although strong associations between PICC exposure, especially to deliver parenteral nutrition, and the risk of bloodstream infection have been described, observational studies have not provided consistent evidence about the effect of duration of PICC placement ('dwell time') on the risk of invasive infection in newborn infants. Some reports indicate an elevated risk of infection when the PICC has been in place for more than about 10 to 14 days, while others do not show any association until after a dwell time of four to six weeks (Smith 2008; Sengupta 2010; Wong 2012; Milstone 2013; Greenberg 2015). Furthermore, it is not certain to what extent PICC use is an independent risk factor for a bloodstream infection or whether observed associations exist because infants who are smaller, less mature, sicker and receiving more intensive and invasive support are also more likely to have a PICC *in situ*. A Cochrane review of randomised controlled trials of PICCs versus peripheral cannulae for delivering parenteral nutrition to neonates did not show an effect on invasive infection rates. Infants with a PICC*in situ* experienced fewer skin break procedures than infants with a peripheral cannula (or series of cannulae) and this may have balanced the overall risk for acquiring bloodstream infection (Ainsworth 2015).

This review examines the evidence from randomised controlled trials that early planned removal within a pre-specified maximum dwell time versus allowing clinicians to determine when the PICC is removed or replaced affects the risk of bloodstream infection in newborn infants. Limited guidance about this issue is available. The 2011 US Centers for Disease Control and Prevention Healthcare Infection Control Practices Advisory Committee guidelines do not specify a recommended maximum dwell time and advise that PICCs should not be routinely replaced to prevent catheter-related infections (O'Grady 2011). This uncertainty is reflected in surveys of practice that identify wide variation between neonatal care centres with regard to PICC insertion and maintenance (Sharpe 2013; Taylor 2014).

We define the maximum dwell time pragmatically as up to two weeks after insertion based on the typical duration of PICC use for infants in most neonatal units and the minimum time that observational studies have shown this to be associated with a rise in the risk of infection (Smith 2008; Sengupta 2010; Wong 2012; Milstone 2013). The intervention is the pre-specified intent to remove or replace the PICC within this time period, and the control is either (i) any permissive approach that does not pre-specify dwell time but that allows PICC removal or replacement based on clinical criteria (including suspected or confirmed bloodstream infection), or (ii) a longer pre-specified dwell time than the intervention.

How the intervention might work

Pre-specifying a fixed maximum dwell time, with planned removal

rather than an expectant approach, may reduce the risk of a PICC being left*in situ* when not actually in use or needed and reduce the overall length of PICC exposure. These effects could lower the risk of bloodstream infection and its associated complications if the PICC is an independent risk factor for infection. This intervention may also plausibly affect nutrient intake, either reducing receipt of parenteral nutrients, or prompting a more rapid progression to full enteral feeding, or both, with potential consequences for acute morbidity (principally the risk of acute necrotising enterocolitis), growth and development.

Why it is important to do this review

Given the potential for the planned duration of placement of PICCs to affect important outcomes for newborn infants, we undertook a systematic review to identify, appraise and synthesise the available evidence from randomised controlled trials.

Related Cochrane reviews

Other Cochrane reviews assess the effects of other strategies including antimicrobial impregnation or antibiotic locks to prevent PICC-related infection in newborn infants, and early removal versus expectant management of PICC in infants with suspected bloodstream infection (Vasudevan 2011; Balain 2015; Taylor 2015). Another review evaluates the evidence for short- versus longer-term use of umbilical venous catheters for newborn infants (Gordon 2016b).

OBJECTIVES

To determine the effectiveness of early planned removal of PICCs (up to two weeks after insertion), compared to an expectant approach or a longer fixed duration, in preventing infection in newborn infants. We pre-specified subgroup analyses by gestational age at birth (Subgroup analysis and investigation of heterogeneity).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised or quasi-randomised controlled trials, including cluster-randomised controlled trials.

Types of participants

Newborn infants who are to have a PICC placed.

Types of interventions

- Intervention: early planned removal after fixed-term use of PICC (up to two weeks after insertion).
- Control: (i) permissive and expectant approach that allows retention of PICC if needed and in the absence of clinical indicators for removal or replacement, (ii) longer fixed-term use of PICC: at least one week longer than the intervention term.

Trials that assessed the effect of a pre-specified intended duration of PICC placement as part of a package of infection control measures (care bundle) were eligible for inclusion but we planned to analyses them separately from trials of discrete interventions.
We did not intend to include trials where the duration of PICC use was related specifically to the infant's progress in enteral feed intake.

Types of outcome measures

Primary outcomes

- Incidence of laboratory-confirmed bloodstream infection confirmed by culture from blood sampled from peripheral sites (not from indwelling catheters) during hospital admission. 'False-positive' results due to skin contaminants are possible, therefore (where data were available), we planned to exclude cases where infection was attributed to diphtheroids, micrococci, *Propionibacteriaceae* or mixed microbial flora. If sufficient data were available, we planned to examine specific infections with these organisms:
    - coagulase-negative staphylococci;
    - other bacteria (Gram-negative bacilli, *S. aureus*, enterococci);
    - fungi.

Secondary outcomes

- Death before hospital discharge and up one year post-term due to all causes.
- Neurodevelopmental outcomes assessed after 12 months post-term using validated tools: neurological evaluations; developmental scores; and classifications of disability, including auditory and visual disability. We defined neurodevelopmental impairment as the presence of one or more of the following: non-ambulant cerebral palsy; developmental quotient more than two standard deviations below the population mean; and blindness (visual acuity less than 6/60) or deafness (any hearing impairment requiring or unimproved by amplification).

- Death or neurological impairment assessed after 12 months post-term.
- Growth: time (days) to regain birth weight and average rate of weight gain (g/kg/day), linear growth (mm/week), head growth (mm/week) and skinfold thickness growth (mm/week) during hospital admission.
- Extravasation injury: subcutaneous extravasation resulting in skin ulceration; 'deep' extravasation resulting in limb swelling; or 'central' extravasation-infusate in the pleural, peritoneal or pericardial space.
- Number of cannulae or catheters used per infant to administer parenteral fluids until full enteral feeding established.
- Days to full enteral feeding.
- PICC leak, obstruction or breakage necessitating removal of PICC.
- PICC-associated thrombosis necessitating removal of PICC.
- Other morbidity developing after enrolment in the trial until discharge from hospital:
    - bronchopulmonary dysplasia (oxygen supplementation at 36 weeks postmenstrual age);
    - necrotising enterocolitis (Bell stage 2 or 3);
    - retinopathy of prematurity, requiring treatment (medical or surgical).

Search methods for identification of studies

We used the standard search strategy of Cochrane Neonatal (http://neonatal.cochrane.org/).

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL, 2018, issue 4), Ovid MEDLINE (1946 to April 2018), OVID Embase (1974 to April 2018), OVID Maternity & Infant Care Database (1971 to April 2018), and CINAHL (1982 to April 2018) using a combination of the text words and MeSH terms described in Appendix 1. We limited the search outputs with the relevant search filters for clinical trials as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We did not apply any language restrictions.
We searched ClinicalTrials.gov and the World Health Organization's International Trials Registry Platform (http://apps.who.int/trialsearch/Default.aspx) for completed or ongoing trials.

Searching other resources

We examined reference lists in previous reviews and planned to search the reference lists of any included studies. We searched the proceedings of the annual meetings of the Pediatric Academic Societies (1993 to 2017), the European Society for Pediatric Research (1995 to 2017), the Royal College of Paediatrics and Child Health (2000 to 2018) and the Perinatal Society of Australia and New Zealand (2000 to 2018). Trials reported only as abstracts were eligible if sufficient information was available from the report, or from contact with the authors, to fulfil the inclusion criteria.

Data collection and analysis

We used the standard methods of Cochrane Neonatal (http://neonatal.cochrane.org/).

Selection of studies

We screened the title and abstract of all studies identified by the above search strategy and two review authors (MG and WM) independently assessed the full-text articles for all potentially relevant trials. We excluded those studies that did not meet all of the inclusion criteria and stated the reason for exclusion. We planned to discuss any disagreements with a third author (AG) until consensus was achieved.

Data extraction and management

Two review authors (MG and WM) planned to extract data independently using a data collection form to aid extraction of information on design, methodology, participants, interventions, outcomes and treatment effects from each included study. We planned to discuss any disagreements until we reached a consensus. If data from the trial reports were insufficient, we planned to contact the trialists for further information.

Assessment of risk of bias in included studies

We planned to make explicit judgements about whether studies were at low, high, or unclear risk of bias across the domains suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We planned to assess the likely magnitude and direction of the bias and whether we considered it is likely to impact on the findings. We planned to explore the impact of the level of bias in sensitivity analyses.

Measures of treatment effect

We planned to analyse the treatment effects in the individual trials using Review Manager 5.3 (RevMan 2014) and report risk ratio (RR) and risk difference (RD) for dichotomous data and mean difference (MD) for continuous data, with respective 95% confidence intervals (CIs). We planned to determine the number needed to treat for an additional beneficial outcome (NNTB) or an additional harmful outcome (NNTH) for analyses with a statistically significant difference in the RD. We intended to conduct intention-to-treat analyses.

Unit of analysis issues

The intended unit of analysis was the participating infant in individually-randomised trials and the neonatal unit (or sub-unit) for cluster-randomised trials.

An infant would have been considered only once in an analysis. We planned to exclude infants with multiple enrolments as we would have been unable to address the associated unit of analysis issues.

For cluster-randomised trials, we planned to undertake analyses at the level of the individual while accounting for the clustering in the data using the methods recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Dealing with missing data

We planned to request additional data from the trialists if data on important outcomes were missing or reported unclearly. Where data were still missing, we planned to examine the impact on effect size estimates in sensitivity analyses using the 'best-worst case scenario' technique.

Assessment of heterogeneity

We planned to examine the treatment effects of individual trials and heterogeneity between trial results by inspecting the forest plots. We planned to calculate the I^2 statistic for each RR analysis to quantify inconsistency across studies and describe the percentage of variability in effect estimates that may be due to heterogeneity rather than to sampling error. If we detected moderate or high heterogeneity ($I^2 \geq 50\%$), we planned to explore the possible causes (for example, differences in study design, participants, interventions or completeness of outcome assessments).

Assessment of reporting biases

Had more than 10 trials been included in a meta-analysis, we planned to examine a funnel plot for asymmetry.

Data synthesis

We planned to use the fixed-effect model in RevMan 2014 for meta-analyses (as per Cochrane Neonatal recommendations). Where substantial heterogeneity existed, we planned to examine the potential causes in subgroup and sensitivity analyses.

Subgroup analysis and investigation of heterogeneity

We planned to undertake the following subgroup analysis:

- very preterm (< 32 weeks) infants (versus infants born > 32 weeks).

Sensitivity analysis

We planned to undertake sensitivity analyses to determine if the findings are affected by including only studies of adequate methodology (low risk of bias), defined as adequate randomisation and allocation concealment, blinding of intervention and measurement, and < 10% loss to follow-up.

'Summary of findings' table

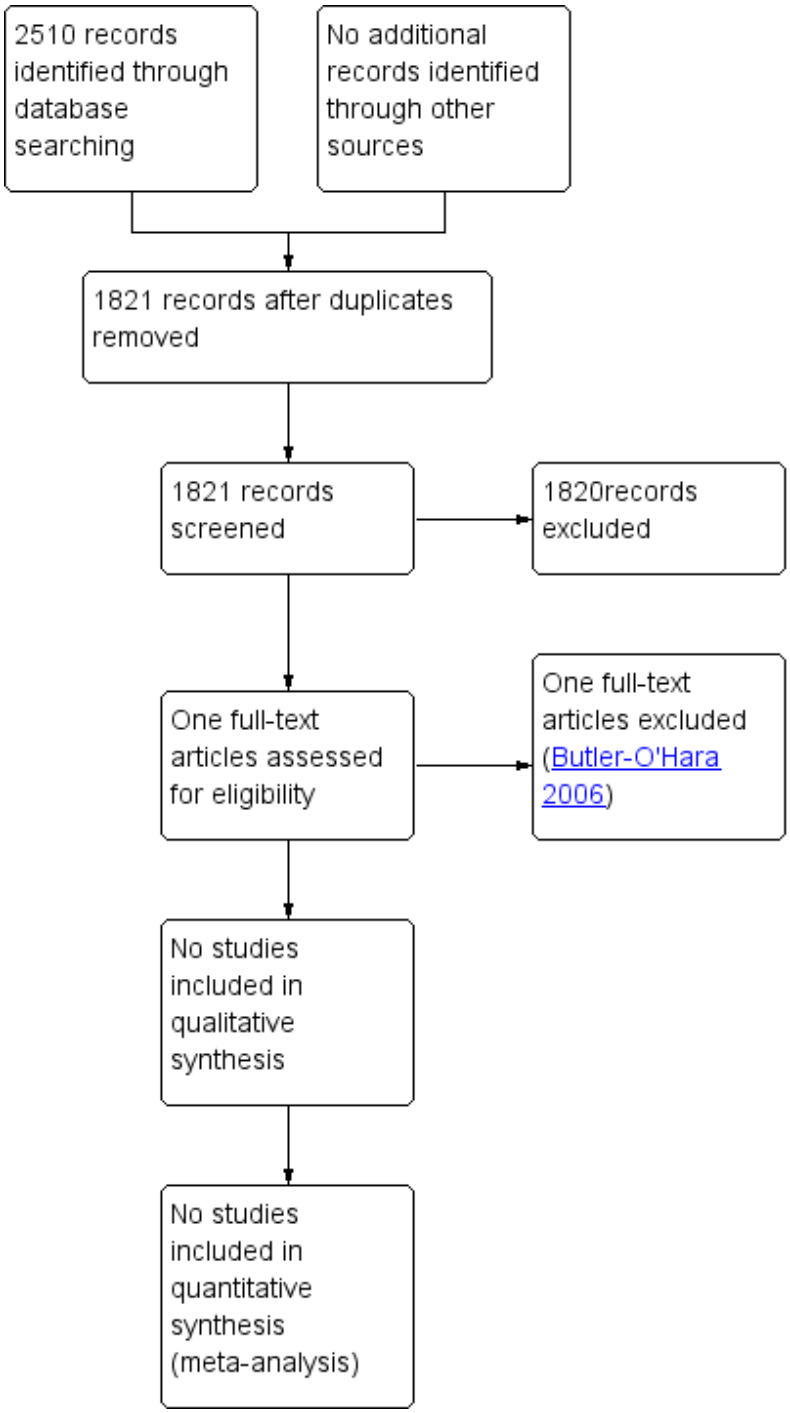
We planned to assess the quality of evidence for the main comparisons at the primary outcomes level using the GRADE approach, as outlined in the GRADE handbook (Guyatt 2011a). Two review authors planned to independently assess the quality of the evidence for outcomes identified as critical or important for clinical decision-making (infection, death). We planned to consider evidence from randomised controlled trials as high quality but downgrade the evidence one level for serious (or two levels for very serious) limitations based upon the following: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates and presence of publication bias (Appendix 2). We planned to use the GRADEpro Guideline Development Tool to create a 'Summary of findings' table to report the quality of the evidence (GRADEpro GDT).

RESULTS

Description of studies

We did not identify any studies or ongoing trials that met our inclusion criteria (Figure 1).

Figure 1. Study flow diagram.



Included studies

We did not identify any eligible trials.

Excluded studies

We excluded one RCT of different durations of placement of umbilical venous catheters in newborn infants (Butler-O'Hara 2006).

Risk of bias in included studies

We did not identify any eligible trials.

Effects of interventions

We did not identify any eligible trials.

DISCUSSION

Summary of main results

Given that deciding the duration of placement of peripherally inserted central catheters (PICCs) is a common and important clinical dilemma that may affect important outcomes for preterm or sick newborn infants, and that substantial uncertainty and variation in practice exists with regard to early planned PICC removal versus expectant management, it is concerning that this question has not yet been addressed in any randomised controlled trials.

Overall completeness and applicability of evidence

In the absence of such trial data, decisions regarding the dwell time of PICCs in infants may continue to rely on the findings of observational studies. These studies, however, have not provided consistent evidence about the effect of duration of PICC placement on the risk of invasive infection and other complications in newborn infants. Any reported associations, moreover, are likely to be confounded because infants who are smaller, less mature, sicker and receiving more intensive and invasive support are both more likely to acquire bloodstream infection and to have a PICC *in situ* (Smith 2008; Sengupta 2010; Wong 2012; Milstone 2013; Greenberg 2015). The variation in policy and practice between neonatal units and clinicians reflects the ongoing uncertainty with which the available observational data are viewed (Sharpe 2013; Taylor 2014).

Potential biases in the review process

Although we conducted a comprehensive search, including conference proceedings, we cannot exclude fully the possibility that other published (but not indexed) or unpublished trials exist.

Agreements and disagreements with other studies or reviews

There appear to be limited data to inform decisions about the optimal duration of placement of PICCs (and other central venous catheters (CVCs)) in other populations of patients. Guidelines published by the Healthcare Infection Control Practices Advisory Committee recommend that PICCs should be removed when no longer essential, but do not recommend *routine* removal and replacement to prevent catheter-related infections, and do not make any recommendations about dwell time (O'Grady 2011).

AUTHORS' CONCLUSIONS

Implications for practice

There are no randomised controlled trials of this intervention to inform policy or practice. Some, but not all, cohort studies suggest that early PICC removal is associated with a lower risk of persistent infection but these findings were not systematically reviewed and should be interpreted with caution because of biases inherent in the study design.

Implications for research

Given the potential for benefit and harm to be associated with the duration of placement of a PICC in a newborn infant, a pragmatic randomised controlled trial of early removal (with replacement if required) versus expectant management may be warranted. Such a trial might primarily address the effect on the risk of catheter-related bloodstream infections (defined using established and validated criteria) in those groups of infants with anticipated prolonged duration of PICC use (such as extremely preterm infants or infants with severe growth-restriction). Trials with sufficient power to detect reliably and precisely effects on the risk of infection and other catheter- and infection-related complications would need to be large, multi-centre and pragmatic in design.

ACKNOWLEDGEMENTS

Ms Kath Wright for developing the electronic search strategy.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Butler-O'Hara 2006	RCT of duration of UVC (not PICC) placement

PICC: peripherally inserted central catheter
RCT: randomised controlled trial
UVC: umbilical venous catheter

CONTRIBUTIONS OF AUTHORS

All authors contributed to the development of this review.

DECLARATIONS OF INTEREST

William McGuire is a co-investigator in a UK multi-centre trial of an antimicrobial-impregnated CVC in preterm infants.

Adrienne Gordon and Mark Greenhalgh do not have any conflicts of interest.

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